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I don't want you to be only
a doctor but I also want you
to be a man
A quotation by His Royal Highness Prince Mahidol of Songkla

the clinical academia

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Our journal is an opened access international journal devoted to peer-reviewed contributions dealing with clinical medicine and medical education from experimental to clinical aspects. Our journal publishes only high quality research, review and other types of original articles, technical and clinical reports every two months. Reviews of various global and Asian aspects will be solicited. Innovation or epidemiological aspects as well as health system research will be addressed. Rigorous systematic review and neglected tropical diseases are our priority

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message from the editor

Medicine is an ever-changing area. This is not because we have so much knowledge, contrary, we know very little. In Pubmed, there are more than 28 million citations. But for a randomized controlled trial with a head-to-head comparison between tramadol and naproxen for pain relief in those with osteoarthritis, we know none. Or even for the route of magnesium sulfate in those with pre-eclampsia, preferred administration route to achieve the therapeutic level is unknown. You can find the answers to the two questions above in this issue. Moreover, you will also find the new invention for diagnosis of cholangiocarcinoma using antigen of its own tumor and case series of infants with gastroschisis. Hope you enjoy reading our journal.

Thammasorn Jeeeraaumponwat, M.D., Ph.D.
Editor-in-Chief of The Clinical Academia

submission

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reviewing process

All accepted articles are classified into two main categories;
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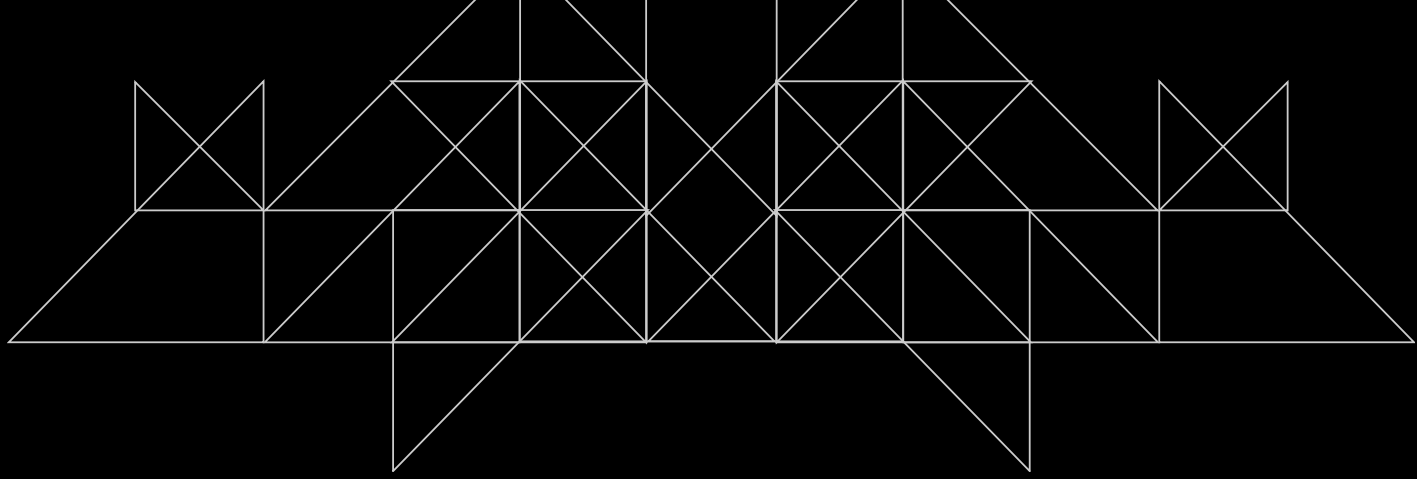
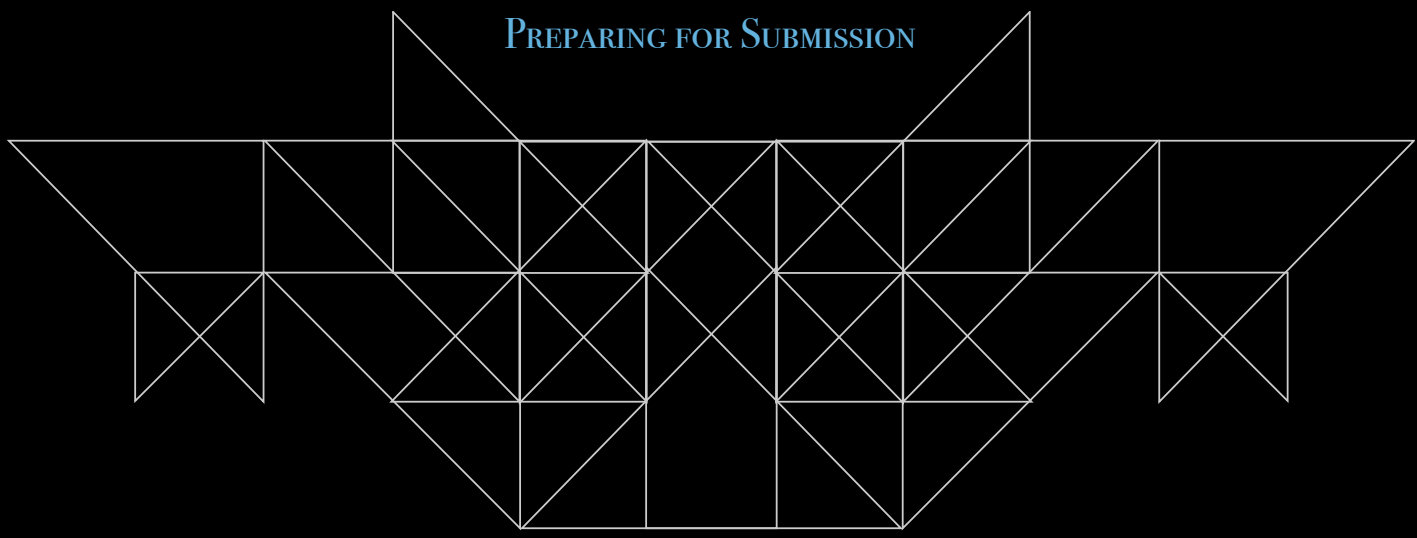
Contents



International Committee of Medical Journal Editors (ICMJE) Recommendation for Preparing for Submission



1. General Principles

The text of articles reporting original research is usually divided into Introduction, Methods, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

2. Reporting Guidelines

Reporting guidelines have been developed for different study designs; examples include CONSORT for randomized trials, STROBE for observational studies, PRISMA for systematic reviews and meta-analyses, and STARD for studies of diagnostic accuracy. Journals are encouraged to ask authors to follow these guidelines because they help authors describe the study in enough detail for it to be evaluated by editors, reviewers, readers, and other researchers evaluating the medical literature. Authors of review manuscripts are encouraged to describe the methods used for locating, select¬ing, extracting, and synthesizing data; this is mandatory for systematic reviews. Good sources for reporting guidelines are the EQUATOR Network and the NLM's Research Reporting Guidelines and Initiatives.

3. Manuscript Sections

The following are general requirements for reporting within sections of all study designs and manuscript formats.

a. Title Page

General information about an article and its authors is presented on a manuscript title page and usually includes the article title, author information, any disclaimers, sources of support, word count, and sometimes the number of tables and figures.

Article title. The title provides a distilled description of the complete article and should include information that, along with the Abstract, will make electronic retrieval of the article sensitive and specific. Reporting guidelines recommend and some journals require that information about the study design be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Some journals require a short title, usually no more than 40 characters (including letters and spaces) on the title page or as a separate entry in an electronic submission system. Electronic submission systems may restrict the number of characters in the title.
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Source(s) of support. These include grants, equipment, drugs, and/or other support that facilitated conduct of the work described in the article or the writing of the article itself.

Word count. A word count for the paper's text, excluding its abstract, acknowledgments, tables, figure legends, and references, allows editors and reviewers to assess whether the information contained in the paper warrants the paper's length, and whether the submitted manuscript fits within the journal's formats and word limits. A separate word count for the Abstract is useful for the same reason.

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b. Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not over-interpret findings. Clinical trial abstracts should include items that the CONSORT group has identified as essential. Funding sources should be listed separately after the Abstract to facilitate proper display and indexing for search retrieval by MEDLINE.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. Unfortunately, information in abstracts often differs from that in the text. Authors and editors should work in the process of revision and review to ensure that information is consistent in both places. The format required for structured abstracts differs from journal to journal, and some journals use more than one format; authors need to prepare their abstracts in the format specified by the journal they have chosen.

The ICMJE recommends that journals publish the clinical trial registration number at the end of the abstract. The ICMJE also recommends that, when a

registration number is available, authors list that number the first time they use a trial acronym to refer to the trial they are reporting or to other trials that they mention in the manuscript. If the data have been deposited in a public repository, authors should state at the end of the abstract the data set name, repository name and number.

c. Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

d. Methods

The guiding principle of the Methods section should be clarity about how and why a study was done in a particular way. Methods section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results. In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.

The Methods section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

i. Selection and Description of Participants

Clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age, sex, or ethnicity is not always known at the time of study design, researchers should aim for inclusion of representative populations into all study types and at a minimum provide descriptive data for these and other relevant demographic variables. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer)." Authors should define how they measured race or ethnicity and justify their relevance.

ii. Technical Information

Specify the study's main and secondary objectives–usually identified as primary and secondary outcomes. Identify methods, equipment (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Identify appropriate scientific names and gene names.

iii. Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size and precision of estimates. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

e. Results

Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods Section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

f. Discussion

It is useful to begin the discussion by briefly summarizing the main findings, and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your finings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly.

g. References

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Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests.Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

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References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses.

References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

ii. Reference Style and Format

References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Sample References webpage and detailed in the

NLM's Citing Medicine, 2nd edition. These resources are regularly updated as new media develop, and currently include guidance for print documents; unpublished material; audio and visual media; material on CD-ROM, DVD, or disk; and material on the Internet.

h. Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

Prepare tables according to the specific journal's requirements; to avoid errors it is best if tables can be directly imported into the journal's publication software. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text.

Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use symbols to explain information if needed. Symbols may vary from journal to journal (alphabet letter or such symbols as *, †, ‡, §), so check each journal's instructions for authors for required practice. Identify statistical measures of variations, such as standard deviation and standard error of the mean.

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For X-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send high-resolution photographic image files. Since blots are used as primary evidence in many scientific articles, editors may require deposition of the original photographs of blots on the journal's website.

Although some journals redraw figures, many do not. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends—not on the illustrations themselves.

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Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce it. Permission is required irrespective of authorship or publisher except for documents in the public domain.

In the manuscript, legends for illustrations should be on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

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k. Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

Tramadol versus naproxen for pain relief in knee osteoarthritis: a pragmatic randomized controlled trial

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To compare the efficacy in term of pain relief between tramadol and naproxen in patients with knee osteoarthritis.

METHODS

We randomly assigned patients with knee osteoarthritis at Khon Kaen Hospital, Thailand to either tramadol or naproxen. The primary endpoint was the pain dimension of Western Ontario and Mcmaster Universities Osteoarthritis Index (WOMAC) at the end of two weeks, the higher scores indicating more severe symptoms. Our secondary endpoints included stiffness, and physical-function dimension of WOMAC scores as well as its total score, serum liver enzymes, creatinine, estimated glomerular filtration rate (eGFR), and their adverse events at the end of two weeks.

RESULTS

A total of 40 patients with knee osteoarthritis; 20 in the tramadol group and 20 in the naproxen group, were qualified for the intention-to-treat analysis. There were no statistically significant differences between the two groups regarding median change of pain of WOMAC score from baseline (-0.8; P=0.90). There was also no statistically significant difference in term of stiffness-WOMAC (0.4; P=0.95), physical function-WOMAC (-0.5; P=0.67), and the total score of WOMAC (2.0; P=0.97). There were no significant differences between the two treatment groups with respect to all secondary endpoints. The frequency of adverse events did not differ significantly between the two groups.

CONCLUSION

We found that the effect of pain relief of tramadol was similar to that of naproxen in knee osteoarthritis. (Thai Clinical Trials Registry (TCTR), 20180216003)

INTRODUCTION

Osteoarthritis (OA), a degenerative joint disease, is one of the most common forms of arthritis which affects around 10% of men and nearly 20% of women in elderly worldwide.[1] It leads to a major cause of disability in elderly.[2,3] As elderly population increases, its prevalence also increases.[4-6] In Thailand, 34.5-45.6% of the elderly suffer from osteoarthritis and knee is the main affected joint.[7-11] Many non-surgical modalities are used to control pain, including pharmacological treatment.[12,13] Oral non-steroidal and inflammatory drugs (NSAIDs) show benefit for pain controlling in osteoarthritis.[14-17] However, gastrointestinal adverse effects from NSAIDs use are also common especially in the elderly[18-19] as well as hepatic and renal toxicity.[20,21] Moreover, there is also the robust evidence of myocardial infarction for long-term use of the NSAIDs.[22-24] Naproxen is claimed to be the most safety NSAID.[25-27] Oral weak-opioid such as tramadol hydrochloride has an efficacy to relief pain in osteoarthritis with less of these side effects.[28,29] However, there is no trial directly comparing efficacy and safety of tramadol and naproxen in those with knee osteoarthritis. The aims of this study was to compare the efficacy in term of pain relief between tramadol and naproxen in patients with knee osteoarthritis.

METHODS

STUDY DESIGN AND OVERSIGHT

This pragmatic, double-blinded superiority randomized controlled trial was conducted as a single center study in Nong Waeng primary care unit, Khon Kaen Hospital, Thailand from October to November 2017.

The protocol was approved by Khon Kaen Hospital Institute Review Board (approval number: KE60043). The study complied with Declaration of Helsinki, October 2013. The protocol of the current study was registered with the Thai Clinical Trials Registry (TCTR), issued number was 20180216003.

RANDOMIZATION

In order to create proper randomization, this study used the permuted-block stratified randomized technique. Two stratified factors were age (<60 years or ≥60 years) and body mass index (BMI) (<23 or ≥23 kg/m^2), patients were randomly assigned into two groups, tramadol or naproxen, in a 1:1 ratio by computer generated using random allocation software, crossover of patient between group were not allowed.

ALLOCATION CONCEALMENT

To keep concealing, the randomized sequence was kept in a sealed opaque envelope. The envelopes were kept in the tray that was locked all the time at the study site. The envelopes were opened at the end of the study.

BLINDING

To keep blinding, tramadol and naproxen were revised into identical empty capsules (500 mg); tramadol was removed from their original capsule and repack in the new capsule and naproxen was ground and fill in the new capsule then contained in bottles. From this process, the patients, the doctors, and the pharmacists were unable to identify the treatment.

PATIENTS

Eligible patients were 20 years of age or older with a diagnosis of unilateral primary or secondary osteoarthritis of the knee defined by the American

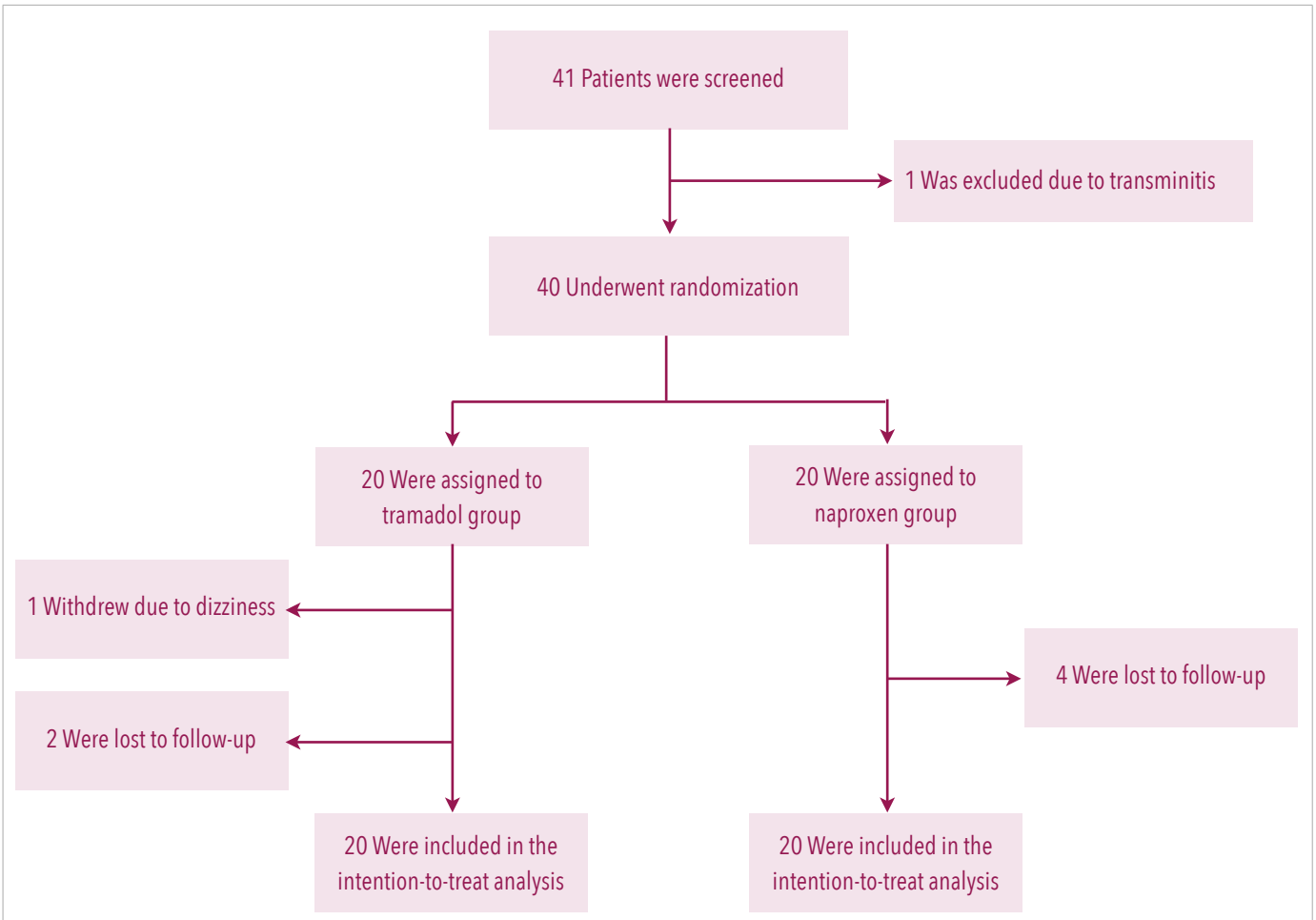

Figure 1. Flow of the study

College of Rheumatology criteria.[30] Patients were excluded if they had used of analgesic e.g., acetaminophen, topical NSAIDs, and topical methyl salicylate or anti-inflammatory drugs including NSAIDs and corticosteroids within one week before recruitment, diagnosed with rheumatoid arthritis, fibromyalgia, ankylosing spondylitis, active gout, pseudogout, or other inflammatory disorder, inflammatory or post-infectious arthritis, previous major knee trauma (knee fracture, knee subluxation/dislocation, neurovascular injury), previous arthroscopic treatment or total knee replacement, previous drug allergy or intolerance for opioid or NSAIDs, history of atherosclerotic cardiovascular disease (ASCVD; stroke, coronary heart disease) or high risk for ASCVD, history of drug or alcohol abuse, history of peptic ulcer disease, from patient or recorded in the patient card, hepatic or renal impairment (AST or ALT above normal range, GFR below 30 ml/min/1.73 m^2),

diagnosis of severe persistent asthma or COPD (uncontrolled symptom with exacerbate everyday), platelet <100,000 mm^3, pregnancy or breast feeding by last menstrual period.

INTERVENTIONS

The patients were assigned into two groups; the intervention group received one tablet of oral tramadol (50 mg) for maximum two times per day, every 12 hours as needed for pain, no rescue medication was allowed and the control group received one tablet of oral naproxen (250 mg) with the same protocol. If they were unable to tolerate the adverse reaction or experienced drug allergy, they were advised to stop taking the given intervention immediately and notify researchers via given contact detail in the patient information sheet.

OUTCOME MEASURES

The Western Ontario and McMaster University Osteoarthritis Index (WOMAC) were used for measure three components of the outcomes: pain, stiffness, physical function of the patients, assessed using a visual analog scale (VAS) ranging from 0 to 10, with higher scores indicating more pain, more stiffness, and more limitation of physical function, respectively. Total score for pain dimension ranged from 0 to 50, stiffness dimension ranged from 0 to 20, physical-function dimension ranged from 0 to 150, summarized to overall score ranged from 0 to 220.31 In the present study, pain-WOMAC at two weeks after randomization was used as the primary outcome. The secondary outcomes were stiffness-WOMAC, physical function-WOMAC and total-WOMAC. Serum liver enzyme; aspartate transaminase (AST) and alanine transaminase (ALT), serum creatinine and estimated glomerular filtration rate (eGFR) at two weeks after randomization were also collected as the secondary outcomes. The safety outcomes were the frequencies of adverse reactions of the individual in the two-week period starting from the randomization. This included rash, nausea or vomiting, abdominal pain, diarrhea, constipation, somnolence, hematemesis, jaundice, and gross hematuria. Suspected of drug allergy were verified by the clinician and pharmacist at the study site. All adverse events were recorded and reviewed by the researcher before the final diagnosis.

DATA COLLECTION

Data regarding baseline characteristic of the patients e.g., sex, age, and body mass index (BMI) were collected at the screening session before randomization. For the outcome, every patient was given the log book containing tables of self-rating VAS, time to take medications, and their adverse reactions. Patients were asked to record baseline pain at the screening session and at two weeks after randomization. Patients were self-recording the time and their adverse event in the log book each time they took the medication. After the end of the study, their logbooks were collected by the researcher for outcome assessment. Blood samples were collected at the screening session and at two weeks after randomization.

STATISTICAL ANALYSIS

The sample size was calculated based on 5% and 20% of alpha and beta errors, respectively with mean difference of pain reduction between the two groups of 1.6 and pooled standard deviation (SD) of 8.1, the total sample size was 40, with the

Table 1. Baseline Characteristics of the Patients.

Characteristic	Tramadol (N=20)	Naproxen (N=20)
Age - yr		
Median	63.0	63.5
Interquartile range	58.3-72.0	54.8-71.0
Male sex - no. (%)	3 (15.0)	3 (15.0)
Body-mass index†	27.1±3.7	26.5±4.1
Primary osteoarthritis - no. (%)	18 (90.0)	15 (75.0)
Duration of osteoarthritis - yr		
Median	1.0	1.0
Interquartile range	0.4-2.8	0.5-2.0
WOMAC*		
Pain		
Median	29.2	28.1
Interquartile range	28.6-39.3	24.0-30.1
Stiffness		
Median	12.2	12.3
Interquartile range	10.0-15.6	11.0-14.3
Physical function		
Median	87.5	88.9
Interquartile range	72.5-108.2	85.6-103.5
Total score		
Median	128.4	102.0
Interquartile range	120.5-154.8	127.4-145.9
Liver function (U/L)		
AST		
Median	23.0	23.5
Interquartile range	21.3-24.0	21.3-25.0
ALT		
Median	20.5	21.0
Interquartile range	16.8-21.0	20.0-23.0
Creatinine (μmol/L)		
Median	0.74	0.74
Interquartile range	0.63-0.80	0.70-0.80

Table 1. (Continued)		
GFR (ml/min/1.73m^2)		
Median	85.8	85.8
Interquartile range	82.9-93.6	81.3-91.8

Plus minus values are means±SD

*Scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were assessed with the use of a visual-analogue scale that ranged from 0 to 10, with higher scores indicating more pain, more stiffness, and more limitation of physical function, respectively.

additional allowance for up to 20% of the loss to follow-up. All data were cleaned before the analyses. The patients' baseline characteristics were presented with number and percentage for categorical variables, mean and standard deviation (SD) for normally distributed continuous variables, and median and interquartile range (IQR) for non-normally distributed continuous variables. The primary and secondary outcomes were expressed in term of between-group median difference from baseline using Mann-Whitney U test, adverse events were described using frequency. A two-sided $P<0.05$ indicated statistical significance. All outcomes were analyzed based on an intention-to-treat basis.

RESULTS

PATIENTS

The patients were recruited during the period from October through November 2017 (Figure 1). All of them were screened at Nong Waeng Primary Care Unit. Of these, one was excluded due to transaminitis, 40 (98%) underwent randomization, 20 to the intervention and 20 to the control group. A total of 33 patients; 17 in the intervention group and 16 in the control group were complete at two weeks. Of these 40, more than three quarters were female, nearly all of them were older than 60 years old with high BMI and diagnosed with primary osteoarthritis for median one year. At baseline, they generally had moderate pain-WOMAC, and their baseline characteristics did not differ significantly (Table 1).

PRIMARY OUTCOME

At the end of the study at two weeks, we found that WOMAC scores were improved in both groups excepted the score on physical function-WOMAC in the intervention group (Figure 2). However, for the primary outcomes, median change of pain-WOMAC from baseline was not statistically different between the two groups (-0.8; P=0.90) (Table 2). We were also analyzed on per protocol basis, these analyses showed consistent non-significant differences between the two groups (-1.4; P=0.78).

SECONDARY OUTCOMES

The same pattern was also observed for the median change of stiffness-WOMAC from baseline between the two groups (0.4; P=0.95), median change of physical function-WOMAC from baseline between the two groups (-0.5; P=0.67), median change of total score-WOMAC from baseline between the two groups (2.0; P=0.97). No significant differences between the intervention group and the control

Table 2. Outcomes

Outcome	Group	Median		Between-Group Median Change from baseline*	P Value	Median		Between-Group Median Change from baseline†	P Value
		Baseline	2 Wk			Baseline	2 Wk		
WOMAC‡									
Pain	Tramadol	29.2	19.3	-0.8	0.90	31.9	25.0	-1.4	0.78
	Naproxen	28.1	19.0			21.9	16.4		
Stiffness	Tramadol	12.2	9.2	0.4	0.95	13.0	9.8	0.3	0.92
	Naproxen	12.3	8.9			11.3	7.8		
Physical function	Tramadol	87.5	72.5	-0.5	0.67	88.1	77.9	7.1	0.63
	Naproxen	88.9	74.4			86.8	69.5		
Total score	Tramadol	128.4	102.0	2.0	0.97	133.1	109.6	6.0	0.75
	Naproxen	128.7	100.3			123.2	93.7		
Liver function (U/L)									
AST	Tramadol	23.0	21.5	0	0.67	23.7	21.8	-1.4	0.71
	Naproxen	23.5	22.0			22.8	22.3		
ALT	Tramadol	20.5	17.5	0	0.69	19.6	16.6	-1.5	0.69
	Naproxen	21.0	18.0			22.5	21.0		
Creatinine (μmol/L)	Tramadol	0.74	0.75	0	0.57	0.72	0.72	-0.02	0.67
	Naproxen	0.74	0.75			0.76	0.78		
GFR (ml/min/1.73 m^2)	Tramadol	85.8	84.7	1.1	0.87	86.9	86.9	2.2	0.59
	Naproxen	85.8	83.6			84.5	82.3		

*From intention-to-treat analysis
† From per protocol analysis

group were found for the change from baseline in secondary outcomes at two weeks (Table 2), the median change in the AST was -1.5 in the intervention group and -1.5 in the control group, a difference of 0 (P=0.67); the median change in the ALT was -3.0 in the intervention group and -3.0 in the control group, a difference of 0 (P=0.69); the median change in the creatinine was 0.01 in the intervention group and 0.01 in the control group, a difference of 0 (P=0.57); the median change in the GFR was -1.1 in the intervention group and -2.2 in the control group, a difference of 1.1 (P=0.87).

ADVERSE EVENTS

The number of adverse events did not differ significantly between the two groups (five events in the intervention group and three events in the control group, P=0.451) (Table 3), no serious adverse events were found. The main adverse event was nausea and vomiting involving two patients each group and constipation which reported by three patients in the intervention group and one patient in the control group. One patient in the intervention group withdrew from our study due to dizziness symptom after taking the medication.

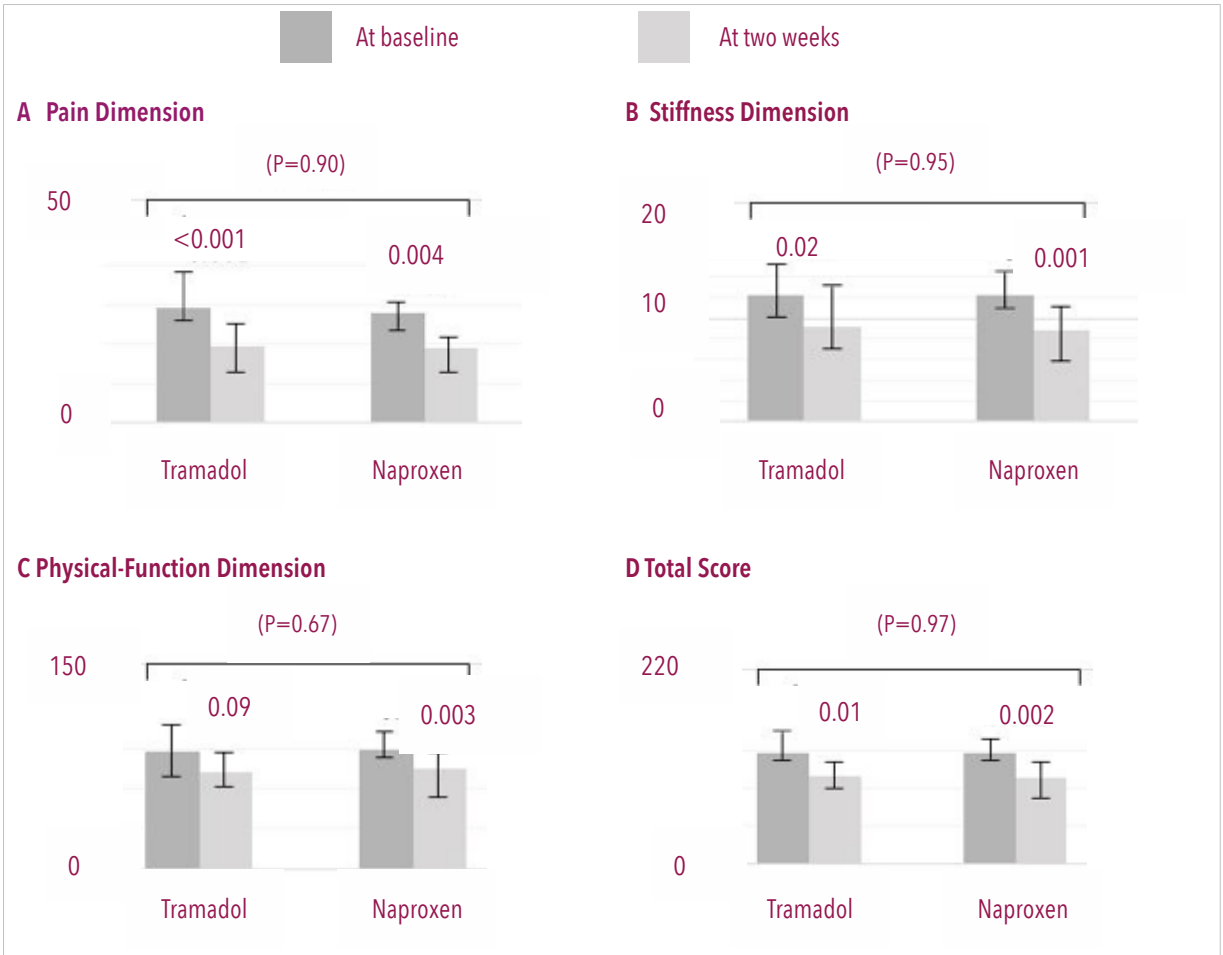

Figure 2. Median changes on WOMAC Score at baseline and after two weeks

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were assessed with the use of a visual-analogue scale that ranged from 0 to 10, with higher scores indicating more pain, more stiffness, and more limitation of physical function, respectively. Panel A is pain dimension, Panel B is stiffness dimension, Panel C is physical function dimension and Panel D is total score. I bars represent interquartile range. P values without brackets are for the change from baseline in each group. P values with brackets are for between-group differences at week 2.

DISCUSSION

MAJOR FINDINGS

In the present study, In the present study, tramadol was representative for weak-opioid and naproxen was for NSAID. Both drugs were analgesics used for mild to moderate pain in the analgesic ladder of world health organization (WHO).[32] We found that the effect of pain relief of tramadol, administered at a dose of 50 mg twice daily as needed for pain, was similar to that of naproxen at a dose of 250 mg. The results were similar regarding the secondary outcomes on stiffness, physical function, and total WOMAC score. Our findings also demonstrated no

Table 3. Adverse events

Event	Tramadol (N=17)	Naproxen (N=16)
	no. (%)	
Overall	5 (26.3)	3 (15.0)
Nausea or vomiting	2 (10.5)	2 (10.0)
Constipation	3 (15.8)	1 (5.0)
Rash	0	0
Abdominal pain	0	0
Diarrhea	0	0
Somnolence	0	0
Hematemesis	0	0
Jaundice	0	0
Gross hematuria	0	0

differences in serum liver enzymes, creatinine, eGFR, and adverse events. This can result in the same effect for pain relief in knee osteoarthritis.

For physical function-WOMAC, similar effects of the two interventions might be due to a short study period. Changes may require longer follow-up as the resolution of inflammation needs more times. For liver and renal outcomes, the AST, ALT, creatinine, and eGFR reflected pharmacodynamics of both drugs. No elevated liver and renal functions were observed explaining by their normal therapeutic range and short study time. Moreover, the patients only took the medication if pain occurred. In safety aspect, the main adverse event was constipation, mostly in the tramadol group, according to the normal gastrointestinal side effect of opioid, followed by nausea which was equally found in both groups.

COMPARISON WITH OTHER STUDIES

In our study, the interventions were able to demonstrate the positive effect on pain, stiffness, physical function of WOMAC even in the short period of time. This was similar to the findings of two previous systematic reviews.[28,29] However, we were the first to directly compare tramadol and naproxen. For magnitude of pain relieving, The effects of our intervention at a dose of tramadol of 100 mg per day were able to show the efficacy and these findings were found at two weeks, compared to other studies in the systematic review which titrate the intervention dosage from 50 to 400 mg per day and most of them measure the outcome on at least four weeks.[28] For the control group, the effect for pain relief at a dose of naproxen of 500 mg per day was also found, compared to previous studies in the systematic review which titrate the

dose equal to exceeding 1000 mg per day on at least 2-13 weeks.[15] In relation to the adverse events of the two interventions, we found no significant increase of serum liver enzymes and creatinine levels. However, no prior study examined these effects of the two interventions on the liver and renal functions. Nonetheless, the findings regarding nausea, vomiting, and constipation, the effects were found more commonly in the tramadol group, supported the findings found from the previous study.[34] The rate of side effect of constipation was closely from our study (15.8%) and a previous study (21%).[34] But for nausea or vomiting, our finding was half from the previous study (10.5% and 24.2% respectively).[34] Withdrew were from minor adverse events and from the loss to follow up similar to the previous studies.[33,34]

STRENGTH AND LIMITATIONS

To our knowledge, this is the first study with the direct comparison of tramadol and naproxen in those with knee osteoarthritis. However, our study held several limitations. Firstly, we did not vary dosages of tramadol and naproxen. Thus, the conclusion was solely based on the mentioned dosage in our study. Secondly, 2-weeks study period was far too short to investigate the outcomes such as physical functions. This required longer follow-up study to envisage the long-term effects of the interventions. Thirdly, we did not perform subgroup analysis due to the small number of the patients. A larger trial should be purposed. Finally, most outcomes were subjective, as the WOMAC score using VAS can be varied due to the patients' perception. Pain threshold was also subjected to be varied.

CONCLUSION AND IMPLICATION

We found that the effect of pain relief of tramadol was similar to that of naproxen in knee osteoarthritis as well as the adverse events. This implied the interchangeability of the two drugs. However, for a robust conclusion of the effects of tramadol and naproxen in knee osteoarthritis, a larger randomized controlled trial with various dosages of both drugs and a longer follow-up time should be conducted.

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Intramuscular and intravenous routes of magnesium sulfate in preeclamptic with severe features transferred from community hospitals: a retrospective cohort

ORIGINAL ARTICLE

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ABSTRACT

OBJECTIVE

To compare the therapeutic level of the two routes of magnesium sulfate ($MgSO_4$) treatment; intramuscular (IM) and intravenous (IV), in the preeclamptic patients during the transfer process from community hospitals to the obstetrics care center, especially in low or high maternal weight group.

METHODS

This retrospective cohort study aimed to compare the rate of the therapeutic level achievement of serum magnesium levels in preeclamptic women with severe features with the two routes of $MgSO_4$; IM and IV, from the community hospitals before transferring to the obstetrics care center at Udonthani Hospital, Thailand. Serum magnesium level at admission and 4 hours at Udon Thani Hospital was taken. The rate of therapeutic serum Mg level achievement, sub-therapeutic, supra-therapeutic level, and adverse effects were also compared between the two routes.

RESULTS

Of these 754 preeclamptic patients with severe features, 285 in the IM group and 469 in the IV group. There were 58.3% of the women in the IM group achieved the therapeutic level compared with 22.2% in the IV group (adjusted odds ratio (AOR) 4.23; 95% confidence interval (CI) 3.01 to 5.94). For the subgroup analysis regarding body weight (BW), those with BW less than 60 kg, 79.3% of the IM group compared with 47.4% in the IV group (AOR 4.01; 95% CI 1.32 to12.2) achieved the therapeutic level; those with BW 60 to 79 kg, 66.7% in the IM group compared with 22.8% in the IV group (AOR 5.48; 95% CI 3.40 to 8.81) achieved the therapeutic level; those with BW 80 to 99 kg, 43.0% in the IM group compared with 15.6% in the IV group (adjusted OR 4.97; 95%CI 2.50 to 9.89) achieved the therapeutic level; and fort those with BW more than 100 kg, 30.0% in the IM group compared with 0% in the IV group achieved the therapeutic level.

CONCLUSION

IM route of $MgSO_4$ was associated with higher rate of therapeutic level achievement than that of the IV route in $MgSO_4$ regimen in preeclamptic women with severe features.

INTRODUCTION

Preeclampsia is a significant cause of maternal death and morbidity around the world, estimated ten million women develop preeclampsia and 76,000 women die each year worldwide.[1,2] Eclampsia is a complication which can lead to maternal death or dreadful maternal outcomes.[3] Magnesium sulfate ($MgSO_4$) is consistently recommended for eclampsia prevention by obstetrics organizations worldwide[4,5], although the $MgSO_4$ action mechanism still remains unclear.[6,7] $MgSO_4$ has been found to be more effective for convulsion prevention than other drugs such as phenytoin, diazepam or antihypertensive drug alone.[8-10] There is no consensus on the route and dosage of $MgSO_4$ administration.[11] However, two commonly used regimens are a 4-6 g of 10% $MgSO_4$ solution intravenously followed by 1-3 g/hour as a continuous infusion[12] (IV route) or 10 g of a 50% solution intramuscularly followed by 5 g intramuscularly every four hours[13] (IM route). The therapeutic drug level of $MgSO_4$ does not have a clearly established concentration threshold for ensuring convulsion prevention. However, the recommended level, based on retrospective data, is 4.8 to 8.4 mg/dL (2.0 to 3.5 mmol/L)[14] and serum Mg level monitoring has been practiced to ensure safety and to avoid toxicity.

The referral process between a community hospital and obstetrics care centers in the provincial or regional hospitals is critical for preeclamptic care. $MgSO_4$ is usually started at the community hospitals to prevent the convulsion. The route of administration is an important factor for achieving the serum therapeutic level. In general, IV route produces serum Mg level consistently, whereas the IM regimen has higher serum Mg level but inconsistently.[15] The best $MgSO_4$ administration route has not yet been clearly evaluated. The objective of this study was to compare the rate of preeclamptic women with serum therapeutic level achievement and avoiding serious side effect for $MgSO_4$ administration by two routes, IM and IV, during the referral process.

METHODS

STUDY DESIGN

A retrospective cohort study was conducted at Udonthani Hospital, Thailand. Preeclamptic patients with severe features who had been transferred from community hospitals to obstetrics care center at Udonthani Hospital from October 2011 to September 2017 were reviewed.

PATIENTS

Medical records of the patients with preeclampsia with severe features were retrieved and reviewed. The preeclamptic was diagnosed, according to American College of Obstetrics and Gynecology 2013 Criteria;[16] a new onset of hypertension (systolic blood pressure 140 mmHg or higher, diastolic blood pressure 90 mmHg or higher plus a new onset of proteinuria (urine protein more than 300 mg in 24 hours or urine protein creatinine ratio more than 3.0 mg/dL). The diagnosis can be made with hypertension with other symptoms such as thrombocytopenia (platelet less than 100,000/microliter), a new onset of renal insufficiency (doubling of serum creatinine or elevated serum creatinine $\geq$1.1 mg/dL in the absence of other

Table 1. Characteristics of the patients

Characteristic	Total (n = 754)	Intramuscular group (n=285)	Intravenous group (n=469)	P Value
Age-year				<0.01
Median	27	26	28	
Interquartile range	21-34	20-32	21-34	
Previous pregnancy-no. %	343 (45.5)	125 (43.9)	218 (46.5)	0.64
Gestational age-weeks				0.03
Median	37	38	37	
Interquartile range	35-39	36-39	35-39	
Body weight-kg				0.99
Median	74	74	74	
Interquartile range	65-85	65-85	65-83	
Height-cm	157.1±6.1	156.9±6.1	157.3±6.0	0.47
BMI-kg/m^2				0.42
18.5 to <25	115 (15.3)	45 (15.8)	70 (14.9)	
25 to <30	251(33.3)	85(29.8)	166(35.4)	
30 to <40	352(46.7)	139(48.7)	213(45.4)	
≥40	36(4.8)	16(5.6)	20(4.3)	
Median	30.1	30.4	30.0	0.47
Interquartile range	26.8-33.7	26.6-34.7	26.9-33.3	
MAP-mmHg				0.52
Median	126.7	126.7	126.3	
Interquartile range	120-132.3	120-132.7	(120-132)	
GFR -ml/min				<0.01
Median	157.4	139.4	169.1	
Interquartile range	122.9-203.4	109.6-191.7	134.7-208.4	

Plus minus values are means±SD; BMI: body mass index; MAP: Mean arterial pressure; GFR: Glomerular filtration rate

renal disease), hepatic dysfunction (elevated serum liver transaminases more than double of the normal concentration), pulmonary edema and a new onset of cerebral or visual disturbances.

The criteria for severe features were defined as preeclamptic patients who had one of the following; elevated blood pressure (systolic blood pressure 160 mmHg or higher or diastolic blood pressure 110 mmHg or higher), elevated creatinine level (doubling of serum creatinine or elevated serum creatinine more than 1.1 mg/dL), impaired liver function (elevated serum liver transaminases more than double of the normal concentration), severe persistent right upper

Table 2. Outcomes of treatments

Outcome	Intramuscular group	Intravenous group	Crude odds ratio	Adjusted odds ratio* (95% CI)
	no. (%)			
Achieved therapeutic level	166 (58.3)	104 (22.2)	4.9	4.23 (3.01 to 5.94)
Body weight<60 kg	23 (79.3)	27 (47.4)	4.26	4.01 (1.32-12.2)
Body weight 60-79 kg	100 (66.7)	56 (22.8)	6.77	5.48 (3.40-8.81)
Body weight 80-99 kg	37 (43.0)	21 (15.6)	4.10	4.97 (2.50-9.89)
Body weight≥100	6 (30.0)	0	NA	NA
Sub-therapeutic level	119 (41.8)	365 (77.8)		
Convulsion during transfer	0	0		

N/A not applicable

*Adjusted for age, gestational age and glomerular filtration rate

quadrant or epigastric pain without other alternative diagnosis, a new onset cerebral or visual disturbances, thrombocytopenia and pulmonary edema.[16] Eclampsia was defined as an occurrence of new onset, generalized, tonic-clonic seizure or coma in preeclampsia patient without the other causes.[16]

EXPOSURES

The protocols for $MgSO_4$ treatment; IV and IM routes were reviewed and recorded. The IV route referred to 4 g of 10% $MgSO_4$ solution IV loading dose followed by 1 g/hr initially. The IM route was 4 g of $MgSO_4$ IV and 10 gm of 50% $MgSO_4$ solution intramuscularly loading dose followed by 5 g intramuscularly every four hours. Serum $MgSO_4$ was monitored at admission and then every 4 hours after the loading dose. Serum Mg levels less than 4.8 mg/dL were considered to be sub-therapeutic and serum Mg levels more than 8.4 mg/dL were considered to be supra-therapeutic.

All patients were monitored for Mg toxicity by deep tendon reflex, respiratory rate, and urine output. The termination of pregnancy was done according to the obstetrical indication. MgSO4 was continued until 24 hours after delivery. This study's exclusion criteria were; pregnancy with myasthenia gravis, pregnant women who delivered at gestational age less than 24 weeks, received $MgSO_4$ in other regimens and cases without serum Mg level recorded.

DATA COLLECTIONS

The demographic data such as age, gestational age (GA), gravity (G), parity (P), blood pressure (BP), mean arterial pressure (MAP), body weight (BW),

height (Ht) , body mass index (BMI), glomerular filtration rate (GFR) were verified and reviewed. The BMI was calculated from the BW and Ht on the delivery day (BW in kilograms divided by the square of Ht in meters). Maternal body weight was classified into four groups; (i) 60 kg or less, (ii) 60 to 79 kg, (iii) 80 to 99 kg, and (iv) 100 kg or more. This classification is made for easy practical use in routine practice.

STATISTICAL ANALYSIS

The patients' demographic data were presented as number and percentage for all categorical variables. The continuous variables were presented by the mean, standard deviation, median, and interquartile range. The data were collected for all participants and categorized for the IV and IM group. The rate for the patients achieving therapeutic level was presented as number and percentage.

A crude analysis was used to determine the effective administration route and other clinical characteristics had on the $MgSO_4$ therapeutic level. Binomial regression and logistic regression analysis were performed to estimate the crude odds ratios and their 95% confidence intervals (CI). The multiple logistic regression analysis and their 95% CI were performed to adjust the effect of other covariate factors with $MgSO_4$ therapeutic level achievement. The magnitudes of effect were presented in terms of adjusted odds ratio (AOR). All analyses were done using Stata 13 (Stata Corp). The significance level was set at $P<0.05$ and all statistical tests were two-sided.

RESULTS

From October 2011 to September 2017, a total of 754 pregnant women composed of 733 preeclamptic patients with severe features and 19 eclamptic patients were transferred from community hospitals to Udonthani Hospital. The distance between hospitals ranged from 30 to 120 kilometers. The time between starting of $MgSO_4$ to serum Mg testing ranged from 50 to 120 minutes. Of these patients, 469 were in the IV group and 285 were in the IM group. The patients' baseline characteristics in each group are presented in Table 1.

The percentages of patients with therapeutic level achievement, at the obstetrics care center, were compared between the IM and IV routes, our study found that 58.3% of IM regimen patients achieved therapeutic level compared with only 22.2% of IV regimen patients. No subject with supra-therapeutic serum Mg was found in either regimen and no convulsion occurred during the referral process in both regimens The covariate factors were adjusted by multiple logistic regression analysis. The IM regimen was found to have the AOR 4.23 times greater than the IV regimen for therapeutic level achievement. The detail is shown in Table 2.

Factors that influenced the therapeutic level for both groups were analyzed. The route and maternal weight were shown to be the factors that affected $MgSO_4$ therapeutic level achievement, as shown in Table 2. The data for patients who achieved the $MgSO_4$ therapeutic level was

classified into four groups according to their maternal BW. The data demonstrated that in all weight groups the IM regimen had a higher rate of therapeutic level achievement. However, in those with BW 80 kg or more, the rate of therapeutic level achievement was less than 50% in both regimens.

DISCUSSION

$MgSO_4$ remains the drug of choice for eclampsia prevention. There is strong evidence proving its effectiveness,[17] However, the proper route and dose in seizure prophylaxis are still controversy.[11] From the current study, the IM route was found to be more effective than the IV regimen during the referral process with 58.2% achieving a therapeutic level at the Obstetrics care center compared with only 22.2% in the IV route. However, the IV loading dose was 4 g, which is commonly used in general practice. A higher loading dose for the IV regimen would still need further evaluation. The IM route also has some advantage in the avoidance of drug administration problem during the patient's transfer. The IV route needs an infusion machine to control the rate of infusion during transfer. It also has to disconnect and reconnect to the IV line during transfer which may cause serious cardiopulmonary problems if the rate of infusion is wrong. However, the IM route cause more pain at the injection site and has a less constant blood level of $MgSO_4$.[15]

Maternal weight is also an important factor. A problem was found in obese women who had a thick layer of fat tissue at the injection site. The recommendation is the use of a longer needle for IM injection. However from this study, even in the higher maternal weight group, the IM regimen was still better than the IV regimen regarding the therapeutic level achievement of $MgSO_4$.

According to maternal weight, the higher maternal weight had a lower proportion of the therapeutic level achievement. Therefore, we advise the adjustment of dosage of $MgSO_4$ according to maternal weight. Women with higher maternal weight should receive a higher dose of $MgSO_4$. The recommended dosage of $MgSO_4$ should be weight adjusted, not to be a single dose for all women. The strength of this study is its large sample size with the focus at the referral time which is the most critical point for the patients. However, the limitation is the retrospective data collection and the use of serum Mg as the measurement outcome. The most appropriate outcome should be seizure avoidance which a very larger sample size is needed to see the differences between these two routes of $MgSO_4$ on this clinical outcome. Moreover, the other confounders such as time between needle to lab might be affected the result.

In conclusion, IM route of $MgSO_4$ was associated with higher rate of therapeutic level achievement than that of the IV route in $MgSO_4$ regimen in preeclamptic women with severe features. However, the strong policy recommendation and implication of the findings of this retrospective cohort should be, however, confirmed with a further prospective randomized controlled trial regarding the effectiveness and the safety of both routes of the preeclamptic patients.

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"The difference between genius and stupidity is; genius has its limits."

— Albert Einstein

Validity of Dot ELISA using crude somatic antigen of cholangiocarcinoma tumor mass

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

to investigate the validity of Dot ELISA using crude somatic antigen of cholangiocarcinoma (CCA) tumor mass.

METHODS

The cross-sectional diagnostic study was performed in patients who admitted at Khon Kaen Hospital, Thailand between October 2016 and March 2017. The overall patients enrolled to collect serum sample was 196 cases. The CHM1, a new prepared somatic antigen was collected and extracted from a liver tumor of one patient which clinically and histopathology confirmed as CCA. The enzyme-linked immunosorbent assay (ELISA) was performed to evaluate the diagnostic performance of reaction with that CHM1 crude somatic antigen.

RESULTS

There were 12 sera of proven CCA which nine sera gave positive results with Dot ELISA. For the 40 sera from healthy donors as the negative control group showed all negative results. We found that sensitivity, specificity, positive predictive value and negative predictive value were 75% (95% CI, 73.6 to 76.4%), 92.9% (95% CI, 91.5 to 94.4%), 40.9% (95% CI,39.5 to 42.3%) and 98.3% (95% CI, 96.8 to 99.6%), respectively.

CONCLUSION

The results showed that Dot-ELISA using CHM1 antigen has a potential for rapid and simple performance to detect antibody in serum of cholangiocarcinoma patients.

INTRODUCTION

Cholangiocarcinoma (CCA) is one of the rare form of cancer with varied prevalence worldwide with the highest rates in the Northeastern Thailand; approximately 80 per 100,000 population.[1] The serum carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) are the most frequently used as serological markers with relatively low sensitivity and high specificity.[2] Other biomarkers such as MMP-9 and TuM2-Pk were also mentioned.[3-5] However, no biomarkers have found to be useful for early diagnosis with no consensus to be used as standard diagnostic tools. Using somatic antigen have been used for serodiagnosis of leptospirosis[6] and the crude somatic antigen prepared from *Fasciola gigantica* found to be a potential for diagnosis of fascioliasis.[7] However, no study has examined the possibility of using somatic antigen from tumor mass for diagnosis of CCA and the use of liver biopsy as antigen is limited by its potential complications, including hemorrhage and tumor spread. In this study, we extracted the tumor mass for somatic antigen preparation by the method of Laemmli[8] and we use Dot enzyme-linked immunosorbent assay (ELISA) using crude somatic antigen of tumor mass of CCA in various sera from various donors. Our aim of the study was to investigate the validity of Dot-ELISA using crude somatic antigen of tumor mass of CCA.

METHODS

STUDY DESIGN AND ETHICAL APPROVAL

The present study was a cross-sectional diagnostic study conducting at Khon Kaen Hospital, Thailand October 2016 through March 2017. Its protocol was approved by Khon Kaen Hospital Institute Review Board (approval number: KE60008). The study complied with Declaration of Helsinki, October 2013.

CRUDE SOMATIC ANTIGEN PREPARATION

The 250 grams of fresh tumor mass which clinically and histologically diagnosed as cholangiocarcinoma was cut into small pieces and washed 3 times with phosphate buffered saline (PBS) pH 7.4 in a petri dish. Then added 50 ml. of PBS and 5 ml of phenylmethylsulfonyl fluoride (PMSF). Then the suspension was homogenized by a homogenizer, then centrifuge for 20 minutes at 10,000 rpm. Gently removed and aspirate the supernatant placed in a new tube, discard the pellet. The protein concentration was 3-5 mg/dl.[9] This preparation was called human cholangiocarcinoma (CHM1) crude somatic antigen. Later the antigen was dotted with 3-5 mg/dl concentration of CHM1 protein coating on the nitrocellulose. The descriptive of this procedure can be found elsewhere.[10]

SERUM TESTING

A total of 196 individual serums using quota sampling were collected from leftover specimens after finish for laboratory testing in Khon Kaen Hospital (Table 1). Of these, 12 cases were histopathologically diagnosed as CCA (positive control), 40 samples from blood donors were used as negative control. We tested all 196 patient's serum with dot-ELISA based on the CHM1 which adsorbed on the nitrocellulose sheet. The nitrocellulose strip was blocked by placing into 5% skim milk in PBS pH 7.4 at room temperature for 10 minutes. Then washed 3 times with PBS. The nitrocellulose strip was incubated with serum sample 0.5 ml in PBS 10 ml. in small box 2 hours on a rotator. After the incubation, the nitrocellulose was washed with

Table 1. Demographic data and clinical characteristics of the specimen donors

Source of specimen	Gander Male:Female	Age	Reaction +/-
Cholangiocarcinomia (positive control)	7:5	52-71	9/3
Surgery Department	38:40	17-57	9/69
Medicine Department	30:26	22-78	0/0
From annual check-up	5:5	35-60	4/6
Blood donors (negative control)	24:16	26-39	0/0

PBS 3 times as described above and then incubated for 2 hours with alkaline phosphatase conjugated streptavidin (1:2,000; Dakopatts). Later, the strip was rinsed three times with PBS and immersed in a substrate solution for color development 10 minutes, washed with distilled water and air dried. The positive reaction appeared as a blue or purplish-blue dot on the test strip distinguishable from the negative as clear spot. The positive and negative control were tested in all run.

DATA ANALYSIS

The validity of the test was calculated regarding sensitivity, specificity, positive predictive value and negative predictive value were analyzed by calculation from a 2x2 table as described by Galens presenting together with 95% confidence interval (CI).[11]

RESULTS

A total of 196 samples were examined using Dot ELISA. The patient's characteristics were shown in Table 1. The positive reaction with 22 serum out of 196 cases. Only 9 cases of positive control from total 12 proven cases demonstrated visualized dot. The same as 40 cases of healthy donor serum showed negative results. Interestingly, 9 cases from patients who admit in Surgery Department showed the positive results, and only 4 cases from check-up individual represented as positive with Dot ELISA.

For validity of the tools in the current studyThe sensitivity, specificity, positive predictive value and negative predictive value were 75% (95% CI,73.6 to 76.4%), 92.9% (95%CI, 91.5to 94.4%), 40.9% (95% CI, 39.5 to 42.3%) and 98.3% (95% CI, 96.8 to 99.6%), respectively.

DISCUSSION

Although our current study indicates that CHM1 may be a potential tool for detection CCA. The need for better tests for detection early stage of CCA is an important issue. However, several studies have reported that many biomarkers served as the tools to diagnose CCA but there is still no specific serum tumor marker as the most potential diagnostic markers for CCA.[2-5] Based on our results in this study, the sensitivity and specificity of anti CHM1 are 75% and 92.93% which demonstrated quite high when compared with CA19-9 (sensitivity

33.0-58.5%, specificity 62.5-84.0%) and CEA (sensitivity 38.0-70.4%, specificity 43.8-98.0%) and for the MMP7 (sensitivity 76.3%, specificity 46.9%). In addition, CA 19-9 levels can rise in other pancreatic and gastric cancers.[13] We suggested that the differences of the patients included in the study should be concerned. In our study, the four patients with no clinical sign of tumor mass in surgery unit gave positive results due to acute cholangitis. So that, it was not clear whether these patients were in the early stage of CCA because it should take a long time to progress as CCA. The subjects in our control group were healthy donors and the annual checkup individuals instead of patients with benign bile duct diseases because of we need to discriminate CCA from a normal population. The utility of molecular techniques on bile samples or brushing material for diagnosis of CCA remains unknown.[12] Interestingly, the study of molecular evidence of CCA should be emphasized because of mitochondrial DNA mutation, whose levels changes during treatment could be potential biomarkers for diagnosis CCA. However, our study provides the CHM1 antigen which is, to our knowledge, the first local antigen preparation to use in Dot ELISA method. This method is one of the non-invasive serological screening tests with relatively high diagnostic value.

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"Turn your wounds into wisdom."

— Oprah Winfrey

Surgical conditions in gastroschisis with feeding intolerance after abdominal closure

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To identify the surgical conditions in patients with gastroschisis with feeding intolerance after abdominal closure.

METHODS

This study was a retrospective case review by verifying and reviewing medical record of those with the diagnosis of gastroschisis between January 2014 and December 2016 at Khon Kaen Hospital, Thailand. All were identified using the hospital inpatient inquiry system with the International Statistical Classification of Diseases and Related Health Problems (ICD) 10 with the code Q79.3. The patients with feeding intolerance were later identified. The surgical conditions and their managements were described.

RESULTS

There were 37 gastroschisis patients; 24 males and 13 females. Their median gestational age was 35 weeks (range, 23 to 39), and median birth weight was 2,200 grams (range, 1300 to 3460). Nineteen of them underwent the primary closure of abdominal wall defects while 17 patients had two-stage repair with silo operation. There were five cases with feeding intolerance requiring additional operations following the abdominal closure. All were caused by mechanical gut obstruction including adhesion band, Hirschsprung's disease, neuronal intestinal dysplasia, jejunoileal atresia and intestinal necrosis at birth.

CONCLUSION

In gastroschisis patients with feeding intolerance after the abdominal closure, mechanical gut obstruction were susupected, additional operations were applied.

INTRODUCTION

Gastroschisis is a congenital abdominal wall defect in which eviscerated stomach and midgut through the defect without membrane coverage.[1-3] The standard treatments are the primary closure of the abdominal wall defect in simple cases and placement of prosthetic silo in the complicated cases.[1-6] The average time from abdominal closure to feeding is approximately 30 days and the average length of hospital stay is about 42 days.[1-3] The condition has a good prognosis with overall survival rate approximately 97.8%.[7] Sepsis is a significant predictor of mortality[7] with only one study describing the mechanical cause of feeding intolerance.[8] This study aimed to identify the surgical conditions related to feeding intolerance in the gastroschisis patients following abdominal closure. Surgical interventions to promote full enteral feeding and some patients' characteristics were also described.

METHODS

STUDY DESIGN

This was a retrospective case review by identifying all medical records of patients with gastroschisis admitted at Kaen Hospital, Thailand between January 2014 and December 2016. The protocol of this study was approved by Khon Kaen Hospital Institute Review Board in Human Research with the approval number of KE60051.

PATIENT RECORDS

All medical records of the patients with gastroschisis were retrieved using the hospital inpatient inquiry system with the International Statistical Classification of Diseases and Related Health Problems (ICD) 10 with the code Q79.3. Later we identified those with feeding intolerance after the abdominal wall defect closure from operation schedule in the operating theater at the hospital and patient medical records. We had no specific exclusion criteria.

DATA COLLECTION

Data regarding basic demographic characteristics e.g., sex, gestational age, birth weight, birth place, mode of delivery, initial procedure for closing the abdominal wall defect were extracted from medical records. The outcomes of treatments including complications, length of hospital stay and discharge status were also collected. Any intra abdominal surgical procedures other than procedures to close the abdominal wall defects were summarized.

STATISTICAL ANALYSIS

All data were entered into a spreadsheet and statistical analysis was performed using Stata 14 software application. For descriptive statistics, categorical variables were summarized using number and percentage. For non-normally distributed variables, they were described using median and range.

RESULTS

Overall, there were 37 gastroschisis patients eligible for the review. There were 24 males and 13 females. Their median gestational age was 35 weeks (range, 23 to 39), and their median birth

Table 1. Characteristics of the patients

Characteristic	Value of 37 cases of gastrochisis
Male-no.	24
Gestational age in week-no.	
23	1
33	5
34	4
35	9
36	6
37	7
38	3
39	2
Median gestational age in weeks (range)	35 (23-39)
Birth weight (grams)-no.	
<1,500	3
1,501-2,000	12
2,001-2,500	12
>2,501	10
Median birth weight in grams (range)	2,200 (1,300-3,460)
Place of birth	
Khon Kaen Hospital	14
Outside Khon Kaen Hospital	23
Route of delivery	
Normal delivery	32
Cesarean section	5
Closing methods	
Primary closure	19
Two stage repair	17
Surgical complications	
No postoperative complications	5
Medical conditions	27
Surgical condition	5
Length of hospital stay(days)	
Median (range)	23.5 (22-40)

Table 1. (Continued)	
Discharge status	
Uneventful	32
Eventful	4
Dead	1

weight was 2,200 grams (range, 1,300 to 3,460). Fourteen gastroschisis patients were born at Khon Kaen Hospital and 23 were referred from other hospitals. Thirty-two were vaginally delivered and five were delivered through cesarean section. The indications for the cesarean section were failed inhibition of delivery (1 case), fetal distress (2 cases), fetal gastroschisis (1 case), premature rupture of membrane (1 case). One case was born before the hospital arrival. Nineteen patients underwent primary closure of abdominal wall defects while 17 patients had two-stage repair with silo operation. One case had bowel gangrene at birth, small bowel resection was performed and palliative treatment was resumed.

Surgical conditions other than abdominal closure were found in five cases and some cases were undertaken additional operation more than one operation as described in Table 2. Initially, all of them had APGAR score 9 and 10 at 1 minute and 5 minutes after birth, respectively. Case 1 and Case 3 were born at Khon Kaen Hospital, the rest were referred from other hospitals.

Case 1 was a male infant born from a primigravida mother. He was a 1,310-gram infant. He had gastroschisis and underwent placement of artificial sac due to there was a large amount of eviscerated contents followed by abdominal closure. He had a problem of feeding intolerance after three weeks after the abdominal closure. He was diagnosed as having an adhesive small bowel obstruction and underwent the exploratory laparotomy with lysis of adhesion band and rectal biopsy at Day 31 after the abdominal closure as his third operation. However, he still unable to tolerate enteral feeding and his abdominal radiography showed the dilatation of the small bowel. The biopsy revealed no ganglion cells in the rectum. Then, he underwent the re-exploratory laparotomy with lysis of adhesion band and colostomy as his fourth operation. He was discharged with the length of stay 115 days. The Final diagnosis was gastroschisis with adhesive small bowel obstruction and Hirschsprung's disease. He was readmitted following 2 weeks of discharge due to diarrhea with salmonella septicemia. He died at Day 10 after the second admission.

Case 2 was a male gastroschisis patient born from a G2P1001 mother. He was 2,680 grams. He had a problem of feeding intolerance after three weeks after the abdominal closure. From the abdominal radiography, it revealed dilatation of the small bowel. He was diagnosed having the adhesive small bowel obstruction. He later had an operation to release adhesion band and full-thickness biopsy was performed with ganglion cells presence from fresh-frozen examination as his third operation. Following the operation, he had

Table 2. Characteristics of the patients

Case	Characteristic	Method of closing abdominal wall defect	Investigation	Surgical conditions	Operation	Date*	Final diagnosis	LOS
1	Male, G1P0000, GA 33 week, birth weight 1,310 grams	Two-stage repair (1st: Silo operation and 2nd closure abdominal wall defect)	Abdominal radiography	Adhesion bands	3rd: Exploratory laparotomy, lysis adhesion band, rectal biopsy	41	Gastroschisis with Hirschsprung's disease	115
			Rectal biopsy	Hirschsprung's disease	4th:Re-exploratory laparotomy, serial biopsy and colostomy	56		
2	Male, G2P1001, GA 37 weeks, birth weight 2,680 grams	Two-stage repair (1st: Silo operation and 2nd closure abdominal wall defect)	Abdominal radiography, rectal biopsy with frozen examination	Adhesive small bowel obstruction	3rd:Exploratory laparotomy, lysis adhesion band with rectal biopsy (presence ganglion cells)	39	Gastroschisis with neuronal intestinal dysplasia	142
			Barium enema		4th:Re-exploratory laparotomy, lysis adhesion band	80		
				Neuronal intestinal dysplasia	5th:Exploratory Laparotomy, lysis adhesion band with colostomy	108		
3	Female, G1P0000, GA 37 weeks, birth weight 2,800 grams	Two-stage repair (1st: Silo operation and 2nd closure abdominal wall defect)	Abdominal radiography	Adhesive small bowel obstruction	3rd:Exploratory laparotomy, division of adhesion band	25	Gastroschisis with jejunoileal stenosis	66
				Jejunoileal atresia	4th:Segmental small bowel resection	43		
4	Female, G1P0000, GA 34 weeks, birth weight 1,700 grams	Primary closure		Bowel gangrene at birth between 10 cm distal to duodeno-jejunal junction and mid transverse colon	Bowel resection with end to end anastomosis (within the same operation of the primary closure the abdominal wall defect)	0	Gastroschisis with intestinal necrosis	17 (refer back)

Table 2. (Continued)

5	Male, G1P0000, GA 35 weeks, birth weight 1,440 grams,	Two-stage repair (1st: Silo operation and 2nd closure abdominal wall defect)	Abdominal radiography	Adhesive small bowel obstruction with jejunoileal atresia	3rd: ,Exploratory laparotomy with small bowel resection with end to end anastomosis	27	Gastroschisis with Jejunoileal atresia	40 (died from pneumonia and septicemia)

LOS, length of hospital stay

*Post operative day of operation after the abdominal closure

recurrence clinical of small bowel obstruction. The barium enema revealed normal study. He, then, underwent re-exploratory laparotomy with lysis adhesion band as his fourth operation. After the operation, he had clinical of small bowel obstruction again. Then, he was diagnosed as having neuronal intestinal dysplasia. He underwent the fifth operation as re-exploratory laparotomy with colostomy and was discharged at 142 days after his admission. He was scheduled for Soave pull through at 13 month-old as the definite surgery with uneventful results.

Case 3 was a female infant diagnosed as gastroschisis.She born at gestational age 37 week from a primigravida mother. Her birth weight was 2,800 grams. Her abdominal wall defect was closed with two-stage repair. The abdominal radiography revealed dilatation of the small bowel. She was diagnosed as having adhesive small bowel obstruction and underwent exploratory laparotomy with lysis adhesion band as her third operation. However, intra-operative findings demonstrated the stricture of jejunoileal segment. Feeding intolerance was still persisted following the operation and the contrast study showed the obstruction at jejunoileal segment. She was later diagnosed as having jejunoileal atresia and underwent segmental small bowel resection as her fourth and definite operation with the total length of stay 66 days.

Case 4 was a female gastroschisis infant born from primigravida mother. She was born through the cesarean section at 34 week of gestational age due to prolong premature rupture of membrane and fetal tachycardia with a birth weight of 1,700 grams. She had gastroschisis with gangrene eviscerated small bowel between 10 centimeters distal to duodenojejunal junction and mid transverse colon. The gangrenous segment was resected with end-to-end anastomosis was performed. The patient was declared as incompatible with life and palliative care was introduced. The length of hospital stay at Khon Kaen Hospital was 17 days.

Case 5 was a male gastroschisis infant born from a primigravida mother at 35 weeks of gestation. His birth weight was 1,440 grams. She was intubated due to respiratory distress since her birth. The two-stage repair was performed. He had wide anterior fontanel and hydrocephalus was diagnosed. At the age of 1-month old, he could not reach full enteral feeding and abdominal radiography showed small bowel dilatation and was diagnosed as having jejunoileal atresia and

underwent exploratory laparotomy with small bowel resection and end-to-end anastomosis as his third operation. He died due to pneumonia and septicemia at the age of 40 days old.

DISCUSSION

This study shows five out of 37 infants with gastroschisis with feeding difficulty after the abdominal wall closure. All were from mechanical obstruction; adhesive small bowel obstruction, bowel necrosis, Hirschsprung's disease, neuronal intestinal dysplasia and jejunoileal atresia. These causes were somehow similar to the report by Florial et al with 185 gastroschisis patients.[8] There was 26% of patients had surgical intervention due to bowel obstruction, anastomotic stricture and bowel necrosis.[8] However, Hirschsprung's disease and neuronal intestinal dysplasia has never been reported together with gastroschisis with feeding intolerance elsewhere. The median time between the closure operation and following operation was found to be 33 days in our study while 60 days in the report by Florial et al.[8] From our findings, any patients with any feeding intolerance after 21 days following abdominal closure should be suspected for other surgical conditions requiring further investigation to minimize parenteral related complications. We found a patient with Hirschsprung's disease presenting with clinical of adhesive small bowel obstruction. It is reasonable to keep in mind that Hirschsprung's disease might be the cause of the bowel obstruction and full-thickness biopsy should be performed. From literature, the overall survival rate is 99% for gastroschisis.[1] Postoperative complication related to wound problems, volvulus, sepsis and adhesion band. In the current study, bowel gangrene was found since birth in one case. Diagnosis of intestinal necrosis, while the fetus in utero was, however, is difficult. Most of the cases in the present study had clinical of adhesion band and contrast study could not clearly identify the point of obstruction.

In conclusion, it is advisable that any gastroschisis patients with prolonged bowel ileus with difficulty in enteral feeding at three weeks after abdominal closure, mechanical obstruction should be aware with further investigations or surgery to promote enteral feeding.

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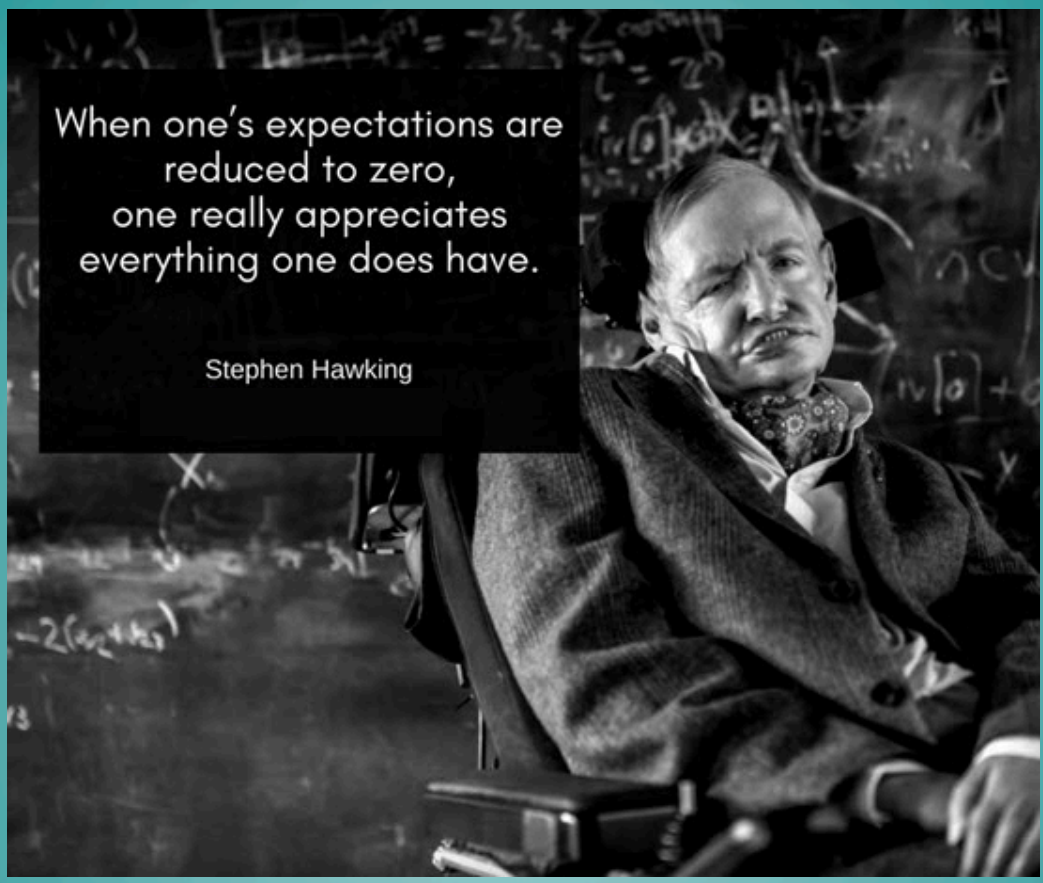
When one's expectations are
reduced to zero,
one really appreciates
everything one does have.
Stephen Hawking

"I shall either find a way or make one"

-Hannibal Barca

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